Population modeling of pre-bronchodilator FEV₁ response to benralizumab treatment in patients with severe asthma

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Objectives: To characterize change of pre-bronchodilator FEV₁ (pulmonary function) from baseline in placebo- and benralizumab-treated patients with severe asthma receiving high-dosage ICS/LABA by using population modeling.

Methods: The population model development was based on the pooled FEV₁ data from 2,244 patients in two pivotal Phase 3 studies, SIROCCO (Lancet. 2016;388:2115–27) and CALIMA (Lancet. 2016;388:2128–41). Empirical exposure-response assessment, population exposure-response and longitudinal modeling of FEV₁ response were conducted. The observed FEV₁ response consists of placebo effect and drug (benralizumab) effect. Longitudinal FEV₁ modeling was conducted in 4 stages: placebo effect modeling, drug effect modeling, baseline FEV₁ modeling and final covariate modeling. Potential effects of demographic and disease covariates on placebo effect, drug effect, and baseline FEV₁ were evaluated by likelihood ratio tests to confirm statistical significance and clinical relevance.

Results: The empirical analysis revealed a flat exposure-response relationship, which was subsequently confirmed by population exposure-response modeling. As such, the pre-bronchodilator FEV₁ data were modelled longitudinally. Standing height and age were identified as relevant covariates for baseline FEV₁ and placebo effect. In addition, baseline FEV₁ was approximately 10% lower in females and in patients on theophylline treatment. Benralizumab treatment was associated with more rapid improvement of FEV₁ (estimated half-maximum time: 7.6 d) than placebo (estimated half-life: 18 d). Estimated typical placebo and benralizumab treatment effects were 184 mL and 96 mL, respectively. Benralizumab efficacy was greater in patients with higher baseline eosinophil counts, with a trend toward improved efficacy in patients with more exacerbations in past year. Benralizumab dose regimen, steady-state pharmacokinetic exposure, presence of anti-drug antibody (ADA), body weight, and concomitant medications did not significantly affect efficacy.

Conclusions: The efficacy plateau for pre-bronchodilator FEV₁ was reached with benralizumab Q8W. This dose regimen minimized the impact of pharmacokinetic variability associated with ADA or heavy body weight on efficacy. No dose adjustment is warranted for any given patient subpopulation.